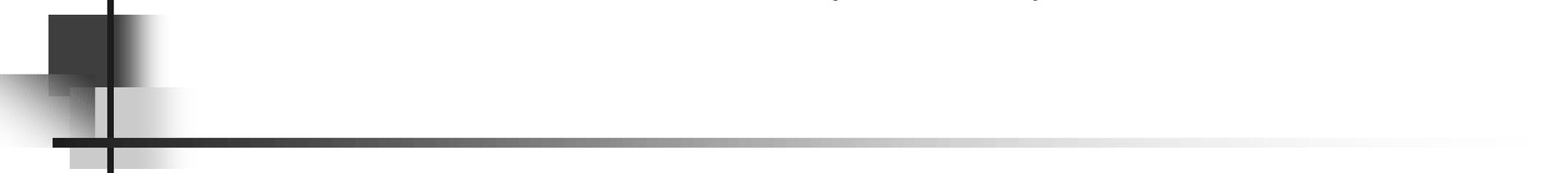
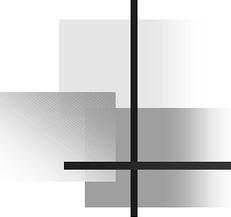


History, Philosophy, the Present and the Future(?) of Randomized Controlled Clinical Trials (RCTs)



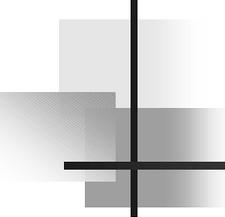
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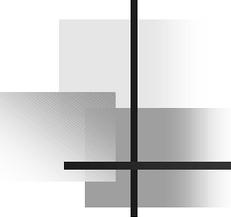
Introduction

- **What is a clinical trial? A medical experiment?**
 - **A study to establish the relative efficacy or effectiveness of treatments for patients to facilitate good medical practice and medical policy.**
 - **Nazi experiments? Tuskegee?**



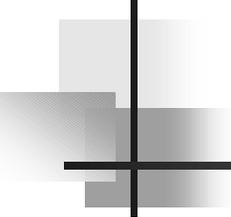
History of Clinical Trials

- **Book of Daniel, 12? Limes to prevent scurvy in the British Royal Navy (1600).**
- **1900–1915: Direct generalization from bench to bedside.**
- **1915–1935: Clinical observation**
- **1935 on: Randomized Controlled Clinical Trails (RCTs)**



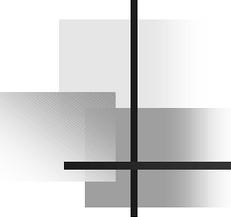
Roots of the RCT

- **Previous experience in clinical trials.**
- **Issues related to causal inferences.**
 - **“Inference”**: drawing conclusions to a population from a sample.
- **Statistical hypothesis testing**
- **Ethical Issues**
 - **“Samaritan” versus “Scientific” ethic**
 - **“Do No Harm!”**



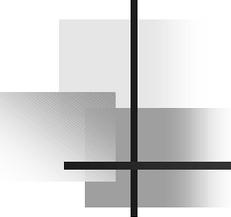
Causality-1

- **To show that T causes O, one needs to show that T precedes O (easy!), T is correlated with O (easy!), and that there is no alternative explanation for the association between T and O (!!!).**



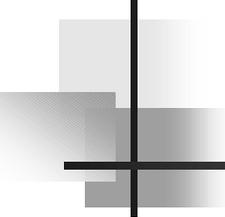
Causality-2

- The causal effect of T on O for an individual subject is the response of that subject if given T compared to the response of the subject not given T.
- This is always a comparative judgment requiring some definition of what is meant by “not given T”: Control or comparison treatment.
- RCT Rule 1: You always need a control or comparison treatment against which T is assessed: C.
- RCT Rule 2: T and C protocols should be well-



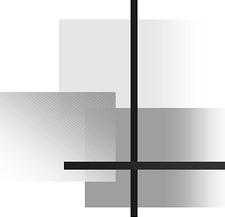
Causality-3

- **Since you can't both give and not give T to a subject at the same time, not feasible to estimate the causal effect on an individual subject.**
- **Ah! Can, however, estimate the average causal effect on subjects in a population, by drawing two random samples from the same population, giving T to one, and C to the other.**
- **RCT Rule 3: You need to sample a specific population of subjects.**
- **RCT Rule 4: You must randomly assign those subjects to T or C.**



Causality-4

- **Must measure same O for both T and C.**
- **Hard, objective measures are fine: e.g. death! Soft, subjective measures are often biased by knowledge of whether a particular patient is getting T or C.**
- **RCT Rule 5: Must have an a priori specified outcome measure.**
- **RCT Rule 6: Objective or blinded measures are required, or some protection against bias.**



RCT “rules” summary

Define the protocols for T and C.

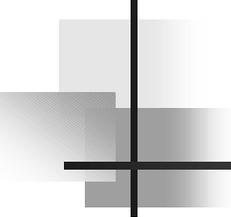
Define the population, and sample it.

Define a response and how to measure it.

Randomize the sample to T and C.

Control for bias by ensuring objectivity or blindness.

A priori rule as to what “proves” that T is better than C.



Problems with the “rules”

What is the appropriate control or comparison?

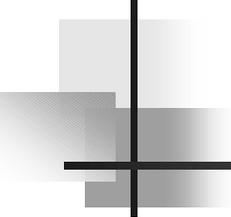
When is a placebo control ethical?

What is the appropriate population?

Biased sample; overgeneralization.

Dropping subjects after randomization

Analysis “by intention to treat”.



More problems with the “rules”

Efficacy versus Effectiveness

Multiple Responses

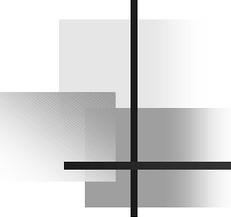
Post Hoc Responses

Poorly measured Responses

**What if you can't blind and don't have
objective measures?**

What if you can't randomize?

**“You can't fix by analysis what you muddle
by design.” Light et al**



Conclusion

RCTs are the “gold standard” of evaluation of efficacy or effectiveness.

The “rules” are strategies that have evolved over a century, reacting to repeated errors.

If you choose to flout the rules, be prepared for the consequences!